



# The Qualitative Value of Facilitated Regulatory Pathways in Europe, USA, and Japan: Benefits, Barriers to Utilization, and Suggested Solutions

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## Abstract

**Background** Despite the growing application of facilitated regulatory pathways (FRPs), little attention has focused on assessing the perception of pharmaceutical companies regarding their usefulness beyond increasing timeliness.

**Objectives** The aim of this study was to characterize the perceived value of four key FRPs, based on industry experiences in using these pathways. In addition, we sought to characterize the perceived impact based on benefits and barriers as well as suggested solutions for their use and recommendations as identified by companies, to outline how these FRPs may be further evolved as tools for expediting the development and regulatory review of important medicines.

**Methods** A study was undertaken to characterize the perceived value and impact of US FDA (i.e., Breakthrough Therapy Designation, Fast Track), European Medicines Agency (i.e., PRIME), and Japanese Pharmaceutical and Medical Devices Agency (i.e., Sakigake) FRPs through a comprehensive analysis of strengths, weaknesses, opportunities, and threats (SWOT) as well as suggested solutions based on industry experiences with their use. The finalized survey comprised six questions and was sent to senior management in regulatory affairs departments at 22 multinational pharmaceutical companies in March 2019, with a deadline for completion by April 2019. The responses were analyzed using descriptive statistics. SWOT and free-text responses were reviewed and manually grouped into key themes according to high concordance.

**Results** Survey results were returned by 11 pharmaceutical companies. Based on their perceived value and positive impact, the evaluated FRPs seem to be generally recognized as helpful tools for ensuring timely development and review of important medicines while ensuring multistakeholder involvement. Respondents overwhelmingly felt that the Breakthrough Therapy Designation carried a positive influence, both within and outside their organizations. Following closely with a positive although varied perception was Sakigake, but respondents exhibited more ambivalence about Fast Track and PRIME. Companies felt the impact of the FRPs was generally positive for most stakeholders except for health technology assessors/payers, highlighting the need to better align FRPs with flexible access and reimbursement pathways to expedite the equitable availability of high-quality, safe, effective medicines.

**Conclusions** This study highlighted common recommendations across all four FRPs (relating to resource optimization, education, alignment, and communication to improve effective use), as well as agency-specific recommendations, some of which are already being addressed by the regulators.

## 1 Background

Facilitated regulatory pathway (FRP) is now a widely adopted term [1] that refers to pathways that offer alternatives to the standard medicines development and registration by accelerating the development, submission, or regulatory review of important medicines. Initially, mature agencies such as the European Medicines Agency (EMA), the US

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## Key Points

Facilitated regulatory pathways (FRPs) have had a documented positive impact on their primary objective of shortening development and review times of important medicines; however, evaluations of their qualitative value and impact are limited. This study identifies the perceived value and impact of key FRPs (i.e., US FDA's Breakthrough Designation and Fast Track, the European Medicines Agency's PRIME, and the Japanese Pharmaceutical and Medical Devices Agency's Sakigake) and potential solutions for barriers to their use.

Company respondents generally considered the studied FRPs as useful tools to facilitate timely development and review of important medicines and involvement of multiple stakeholders, especially the US Breakthrough Therapy Designation and Japanese Sakigake.

FDA, and Japan's Pharmaceuticals and Medical Devices Agency (PMDA) introduced pathways to speed the regulatory review process timelines. More recently, these agencies introduced FRPs that aim to not only speed the review but also help expedite the development of important new medicines (e.g., generally medicines that have the potential to meet an unmet need for a serious or life-threatening condition). These FRPs include FDA Fast Track and Breakthrough Therapy Designation (BTD) introduced in 1997 and 2012, respectively; PMDA Sakigake, launched in 2015; and EMA Priority Medicines (PRIME) in 2016. Others, such as the EMA Conditional and Exceptional Circumstances Marketing Authorizations, FDA Accelerated Approval, and PMDA Conditional Early Approval also offer routes to grant approval for medicines based on initial data that demonstrate plausible clinical benefit or on an unvalidated surrogate or intermediate endpoint, in which the applicant is required to provide comprehensive clinical data in the future that demonstrate actual clinical benefit and a maintained positive benefit-to-risk profile. Details regarding each of these programs are summarized in agency guidances [2–4] and have also been described in recent publications, including the impact of FRPs on time [5–10].

The various FRPs may contribute to shorter development and review timelines by encouraging early dialog between companies and agencies, regulatory guidance on the development program from agencies, increased frequency of updates based on evolving safety–efficacy data in the context of unmet need, and reduced cycle times for regulatory feedback. An additional and important goal for these pathways was to shift the perception of regulators from being primarily “gate-keepers” who keep unsafe and ineffective products off the market to also being “enablers” of

true innovation, where urgency to meet patient need drives progress in approving new therapeutic options for unmet medical conditions [11]. FRPs are therefore key in ensuring timely development and regulatory review of medicines for unmet medical need, as well as in a crisis situation, such as a pandemic.

Nevertheless, studies evaluating the impact and value of FRPs are limited. In one study of basic principles, Liberti et al. [1] assessed survey-based feedback from regulators, health technology assessment (HTA) bodies, pharmaceutical companies, patient advocacy groups, and academia around their perception of FRPs. This first-pass inquiry focused on perceived strengths and weaknesses of key FRPs, including the concept of an “adaptive licensing pathway”. At that time, the following impediments to the widespread use of FRPs were articulated as

- reluctance across all of the stakeholders to make decisions based on clinical study designs where the primary outcome involved a novel endpoint that required full clinical substantiation at a later date;
- perceived lack of commitment on the part of some regulatory and HTA agencies to develop and implement FRPs; and
- skepticism that sponsors, regulators, and HTA/payers were actually collaborating effectively and accurately to define the value characteristics required of new products.

Almost a decade later, and despite the growing application of FRPs [5], little attention has been focused on assessing how the availability and usefulness of FRPs are perceived by pharmaceutical companies, particularly pathways introduced by FDA, EMA, and PMDA to prioritize promising drug candidates for diseases lacking satisfactory treatments, namely FDA BTD and Fast Track, EMA PRIME, and PMDA Sakigake designation. Such information can be helpful to agencies as they look to further revise and improve their FRP processes. In addition, it is crucial for pharmaceutical companies to stay informed regarding the key benefits compared with the resources required as well as other internal considerations that need to be taken into account when deciding which FRPs to pursue for a particular product. Therefore, this study was undertaken to characterize the perceived value of key FRPs through a comprehensive analysis of strengths, weaknesses, opportunities, and threats (SWOT), based on industry experiences in using these pathways. In addition, we sought to characterize the perceived impact based on benefits and barriers as well as suggested solutions for their use and recommendations as identified by companies, to outline how these FRPs may be further evolved as tools for expediting product development and regulatory review of important medicines.

## 2 Methods

### 2.1 Scope

The focus of this survey was on FRPs designed to facilitate the development of important medicines, namely FDA BTD and Fast Track, EMA PRIME, and PMDA Sakigake designation. This survey was not intended to provide details of the processes underlying each FRP, as these are already documented, but to provide a sense of the perceptions of the benefits and difficulties of utilizing these FRPs based on company experience. For the purpose of clarity, it should be noted that the difference between FDA Fast Track and BTD is that BTD drugs must show early clinical evidence of substantial improvement over existing therapies, and the benefits are the same as with Fast Track but with an even greater emphasis on early meetings and coordination with experienced and senior FDA personnel [3].

### 2.2 Survey Design and Participants

A questionnaire was developed by the Centre for Innovation in Regulatory Science (CIRS) and reviewed for clarity and completeness by two multinational pharmaceutical companies. Minor editorial changes were made as a result of a pilot study. The finalized survey comprised six questions (see the electronic supplementary material [ESM]) and was sent to senior management in regulatory affairs departments at 22 multinational pharmaceutical companies in March 2019, with a deadline for completion by April 2019. The companies selected were CIRS member companies and were all international companies that develop innovative medicines across a wide range of therapeutic areas, molecular types, and advanced therapeutic products, thereby making the sample representative [12].

### 2.3 Data Processing and Analysis

The responses were analyzed using descriptive statistics. SWOT and free-text responses were reviewed and manually grouped into key themes according to high concordance.

## 3 Results

### 3.1 Part 1: Company Experience and Strategy

Of the 22 companies, 13 (59%) expressed interest in responding but two were not able to complete the survey by the deadline, therefore, 11 companies completed the questionnaire (50%), ten of which were considered to be in the

top 25 pharmaceutical companies globally, based on 2018 research and development expenditure.

Of these 11 companies, ten had experience with FDA FRPs and PMDA Sakigake and eight with EMA PRIME. Figure 1 summarizes the company experience with the various FRPs. The respondents experienced a high degree of success in applications (receiving the designation from the agency) for the two FDA FRPs compared with EMA and PMDA pathways (10/10 with both US pathways compared with 4/10 for both EMA and PMDA pathways). No company operated on the premise that all development programs would use an FRP; in all cases, companies reported that the decision to apply for an FRP was made on a case-by-case basis. Nevertheless, the majority of companies are currently developing medicines with plans for requesting the use of a single pathway or in combination with multiple FRPs within and across countries.

For companies that received a regulatory approval for a product that used any of the target FRPs, three indicated that the use of that FRP was reflected in their organizations' advertising or promotion to demonstrate the initial promise of the medicine to target unmet medical need (three companies for FDA BTD, two for Fast Track, and two for PMDA Sakigake). Comments provided by respondents indicated that this was generally reflected in a press release or other public communication but not in labeling or other regulatory documentation.

### 3.2 Part 2: Impact and Value of Facilitated Regulatory Pathways (FRPs)

Companies were asked whether they believed the FRP designation impacted how the product was perceived by different stakeholders: the company itself, patients, physicians, other regulators, HTA bodies/payers, and investors (Table 1). Respondents overwhelmingly felt that the BTD carried a positive influence both within and outside their organizations. The second-highest number of positive perceptions were for Sakigake. Respondents exhibited more uncertainty about the perceived value of Fast Track and PRIME. Across all the FRPs, the impact was generally perceived as positive among all the stakeholders. However, respondents felt that FRPs may have a negative or ambivalent impact with HTA/payers.

The overall value for the sponsor for each FRP (Fig. 2) was highest for FDA BTD and Sakigake and was supported by comments indicating the benefits of increased communication with the agencies and the real potential for accelerated development timelines. PRIME's lower score resulted from the perception that not all assets are treated with the same urgency as they are with FDA BTD. FDA Fast Track received the lowest but most consistent scores. The SWOT

analyses in the following section support these overall perceptions.

### 3.3 Part 3: Respondent Reflections on the Strengths, Weaknesses, Opportunities, and Threats of FRPs

Companies completed a SWOT analysis for the four FRPs. Table 2 provides an overall SWOT analysis across the four different pathways. Overall, respondents felt that FRPs offer important benefits, most notably the opportunity for early information exchange and guidance available through these FRPs. Such interactions help resolve uncertainties regarding regulatory expectations, ultimately shortening development and assessment times [3].

These benefits are counterbalanced by the high level of time and workforce commitment required of the sponsor. In addition, as FRPs often provide a path to shorten development time, the process of evidence collection shifts to the post-approval period, which can be a labor-intensive and costly endeavor using sometimes novel research approaches.

Moreover, agencies may not be staffed appropriately to address the required workforce contributions and statutory timelines. Nevertheless, respondents recognized that FRPs offer important opportunities to improve the effectiveness and efficiency of the development and review process through increased dialog, especially with stakeholders such as health technology assessors. They perceived that a “halo effect” (where a product approved in one jurisdiction with an FRP designation benefits from this designation in the review in subsequent jurisdictions) may also lead to reduction of review times in other jurisdictions.

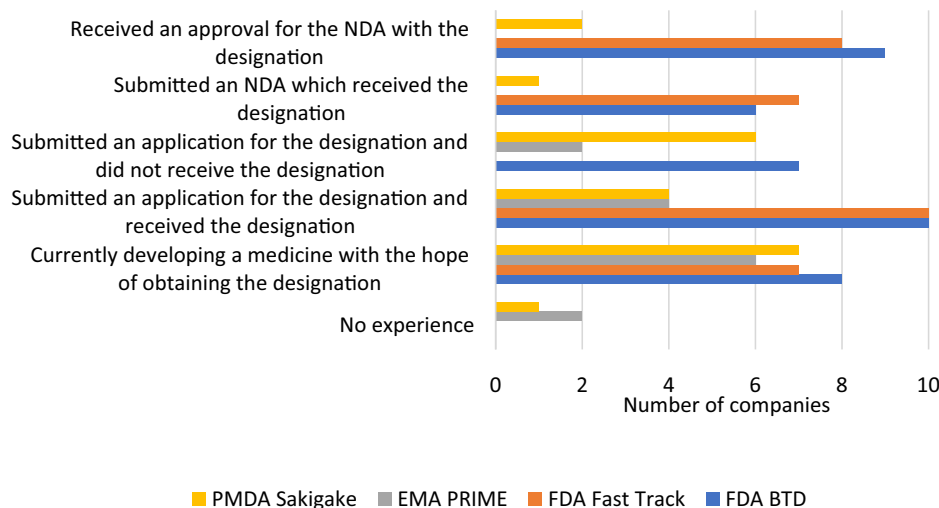
Respondents also completed a SWOT analysis for each pathway; key findings based on perceptions from the participating companies are summarized in the following sections

(Summary SWOT analyses for each FRP are included in the ESM).

- The US FDA: The BTD program provides intensive early FDA guidance from experienced and senior-level agency reviewers on development plans, a higher likelihood for priority and/or rolling review and acceptance of flexible approaches, and a high probability for approval during the first cycle of review. However, the number of competitive applications means the bar for acceptance into the program is high and is getting higher, especially for oncology products. Because clinical data are not required to receive Fast Track designation, applicants have a clear picture as to the likelihood of the designation being granted. However, although there is at least the potential for greater company–agency interaction and expedited or rolling review, the perception that this pathway is of lower priority than BTD, where the benefits are also less clear, make some question its future. Recommendations from respondents were as follows:

- The FDA should further facilitate cross-division and cross-therapy communication regarding alignment of FRP adoption to ensure consistent approaches and criteria for accepting the designation applications across divisions and therapy areas.
- The FDA should consider adopting the principles of “real-time oncology review” across all therapeutic areas for the review of key clinical raw data and analysis before application submission, particularly for Fast Track, which is becoming less relevant.
- The **EMA PRIME** pathway increases opportunities for multistakeholder face-to-face meetings, enhanced rapporteur engagement, and continuity of advice. Unfortunately, the small window of time for application and

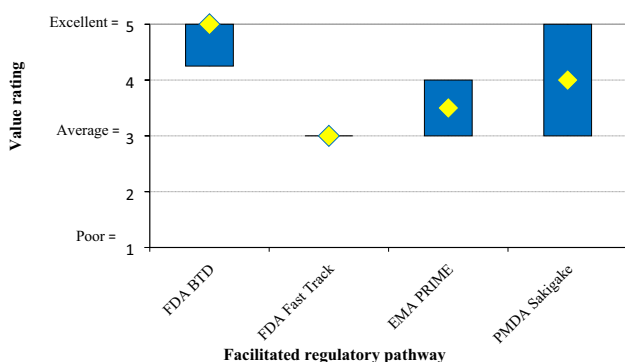
**Fig. 1** Company experience using facilitated regulatory pathways: US FDA Fast Track and Breakthrough Therapy Designation (BTB), European Medicines Agency (EMA) Priority Medicines (PRIME), and Japanese Pharmaceutical and Medical Devices Agency (PMDA) Sakigake. *NDA* new drug application



**Table 1** Companies’ perception on the impact of the FRP designations on how the product is perceived by different stakeholders

	Stakeholder perception																							
	Your company				Patients				Physicians				Other regulators			HTA/payers			Investors					
	-	-/+	+	0	-	-/+	+	0	-	-/+	+	0	-	-/+	+	0	-	-/+	+	0				
FDA BTD			10				9		2	6			1	7	1		5	3	1		1	8		
FDA fast track	3		7		3	3	2		4	2	1		2	3	2		4	2	2		2	4	2	
EMA PRIME	4		4		2	5	1		4	2	1		2	4	1		5	1	2			7	1	
PMDA Sakigake	3		7		2	7			2	7			2	4	2	1		2	3	2		1	7	1

– indicates negative impact, -/+ indicates mixed impact, + indicates positive impact, 0 indicates no impact, blank spaces indicate no responses, *BTD* breakthrough therapy designation, *EMA* European Medicines Agency, *FRP* facilitated regulatory pathway, *HTA* health technology assessment, *N* number of respondents out of ten for FDA BTB, Fast Track and PMDA Sakigake, and out of eight for EMA PRIME, *PMDA* Pharmaceutical and Medical Devices Agency., *PRIME* priority medicines



**Fig. 2** Companies’ scores in terms of overall value for the various facilitated regulatory pathways (FRPs). Box: 25th and 75th percentiles; diamond: median. *BTB* breakthrough designation, *EMA* European Medicines Agency, *PMDA* Japanese Pharmaceutical and Medical Devices Agency, *PRIME* priority medicines

the lack of availability for new indications or for large companies with products in early development results in a relatively low rate of acceptance and a consequent limitation for agency experience. Recommendations from respondents were as follows:

- To promote the better use of resources, the EMA should provide more rapid scientific advice timelines for PRIME products that include early planning and a list of issues to be discussed at a face-to-face meeting (≤40 days vs. the current 70 days).
- The EMA should initiate the opportunity for iterative data submission for PRIME similar to the FDA rolling reviews as well as offer PRIME to large companies and for products later in development.

**Table 2** SWOT analysis by companies – overall impression of FRPs

Strengths	Weaknesses
Focus on unmet medical need and serious diseases	Medicines made available via conditional mechanisms may prove ineffective
May offer multistakeholder involvement	Highly labor intensive for both the sponsor and the agency
Innovative medicines are reaching patients faster with a high level of confidence around their benefit-risk profiles	Require significant investment in post-approval monitoring and commitments
Expedited timing of agency feedback and the overall review process	Greater difficulty valuing drugs that have less clinical information available at launch
Opportunities	Threats
Increased opportunities for agency-company interactions and scientific advice	Add complexity to coordination of global development programs
Opportunity for alignment of regulators, HTA bodies and companies (e.g., PRIME and BTB)	Poor documentation of specific requirements and criteria for receiving a designation
“Halo effect” on global development; may reduce review times in other jurisdictions for products undergoing initial FRPs	Some agencies are becoming overwhelmed by the number of FRP applications
	FRPs shift significant workforce away from standard drug reviews (non-FRPs)

*BTB* breakthrough therapy designation, *FRP* facilitated regulatory pathway, *HTA* health technology assessment, *PRIME* priority medicines, *SWOT* strengths, weaknesses, opportunities, threats

- **PMDA Sakigake** products undergo priority rolling regulatory review with consistent support, have strong positioning as first-in-class innovative products with an extended exclusivity period, and command premium reimbursement prices. However, Sakigake requirements that the product be a first-in-world regulatory submission and the limited acceptance of English documents presents challenges to the development of a global unified dossier. Recommendations from respondents were as follows:

- The PMDA should evaluate unmet medical needs in Japan, increase the window of Sakigake opportunity beyond once-yearly submission, and allow the good manufacturing practice inspection application submission after filing, with the protocol for process validation reviewed in advance.
- The PMDA should promote the globalization of CMC documents and Japan pharmacopoeia, exercise flexibility in accepting global clinical data and joining multinational clinical studies; accept submission of the CTD in English and relax the Japan-specific requirement for CTD preparation, and reconsider criteria for Japanese first-in-world filing.

## 4 Discussion

FRPs can expedite the product development and regulatory review of medicines by providing alternatives to the timing and data comprehensiveness in standard product development and regulatory review routes prior to authorization, with the understanding that further data will be developed to either confirm or refute the plausible benefit upon which the authorization was based. While the ultimate goal is to expedite patient access to safe, effective, quality medicines for high unmet needs [13], including in crisis situations, such as with the current coronavirus disease 2019 (COVID-19) pandemic [14], this remains a challenge as the outcomes of FRPs are not always widely embraced by HTAs and payers because of the uncertainty around the effectiveness of such treatments.

Understanding both the perceived value and the impact associated with FRPs remains a topic of interest to both companies and authorities. This is particularly key with recent COVID-19-stimulated changes in the regulatory landscape, which supports the need for more flexible approaches. An example is a relatively recent shift of the proportion of the overall pharmaceutical development portfolio from small molecules or antibody-based programs to newer therapeutic modalities, which do not lend themselves well to the timing and comprehensive data requirements of traditional

decision-making milestones inherent in development plans anchored in progression from phase I, II, and III [15].

The breadth of adoption and cumulative impact of the use of FRPs on time to approval has been well-documented [5–10]. In general, the findings demonstrated that FRPs, particularly the FDA Fast Track and BTd, had a positive impact on shortening both the development and the review times of important medicines, especially when these address an unmet medical need. However, the qualitative value of such pathways to stakeholders has been less studied [1].

This is the first study to systematically gauge the perception of FRPs by the pharmaceutical industry. The aims were to understand the qualitative value of newly introduced FRPs in Europe, the USA, and Japan, namely EMA PRIME, FDA BTd and Fast Track, and PMDA Sakigake, to identify their perceived benefits, barriers, and recommendations for their utilization to further support expedited product development and regulatory review of products for which it is plausible they may meet an unmet medical need in a serious or life-threatening condition.

Based on the perceived value and positive impact, these FRPs seem to be generally recognized as helpful tools by companies for ensuring facilitated and timely development and review of important medicines while ensuring multi-stakeholder involvement. Respondents overwhelmingly felt that the BTd carried a positive influence both within and outside their organizations. Following closely with a positive perception was Sakigake, although the perception was more varied, which may be because this pathway has only been introduced recently [16]. Respondents exhibited more ambivalence about the perceived value of Fast Track and PRIME, where for PRIME this may also be due to the novel nature of this pathway [17], while for Fast Track the opposite is true where the value of this older FRP seems lower compared with the newer BTd. Across all the FRPs, the companies believed the impact of the designation on stakeholder perception of that product was generally positive for most stakeholders (their own company, patients, physicians, regulators, and investors) except for HTA/payers, where it was mixed. The company perception may be as a result of high uncertainty around the effectiveness of such treatments that HTA agencies and payers may be concerned to accept [18, 19]. This also highlights the need to better align accelerated regulatory pathways with flexible access and reimbursement pathways to expedite the equitable availability of high-quality, safe, and effective medicines that provide a value-based approach to meeting society's most important healthcare needs [20].

### 4.1 Recommendations for the FRPs

Perceived weaknesses and threats (challenges) for the four FRPs engendered some common recommendations, which

if implemented, could further improve the effective use of these pathways. These have been categorized into four themes:

#### 4.1.1 Augment and Optimize Resources

Survey respondents all cited company and agency resource constraints as impediments to the best use of FRPs. Extra company resources are required for the early preparation of submission packages, expedited manufacturing readiness, and ongoing agency communication. Competition for agency FRP resources has increased the level of evidence required for program acceptance, and resources used for FRPs may be prioritized away from important non-FRP products.

- Regulatory agencies should improve and accelerate recruitment of more and experienced reviewers; currently these designations do not normally carry any additional user fees to pay for their added resource and perhaps this could be explored with industry.
- Companies should commit to the early dedication of necessary internal resources for chemistry, manufacturing, and controls development; support for an early submission; the need to rapidly scale up manufacturing; and the ongoing technical support for agency communication.
- Companies should provide frequent updates to agencies regarding product status and upcoming milestones to enable accurate agency resource planning.

#### 4.1.2 Educate Stakeholders

The respondents viewed that the public may not understand FRPs and perceive those as ways to lower regulatory review standards. This may cause a lack of confidence among some healthcare stakeholders, including patients, healthcare professionals, and health technology assessors, resulting in reduced or delayed use and reimbursement of innovative medicines.

- Companies should develop and maintain a program of communication and education to all stakeholders regarding the importance of early-access medicines and their potential for substantial improvement over existing therapies.
- Regulatory agencies should develop and maintain a program of communication and education to all stakeholders around the contextual, iterative benefit-risk assessments that form the basis of the FRP review processes, including withdrawal of FRP designation for products with non-supportive emerging data.

- Companies and agencies should aggregate FRP experience data to publicize the benefits of FRPs.
- Companies and regulatory agencies should support collaborative multistakeholder interactions with HTA bodies and payers to align on the definitions of unmet medical need, evidentiary requirements for the use of FRPs, and learnings regarding earlier regulatory and HTA decision making.

Finally, although not raised specifically in the survey, HTA bodies should also continue to consider how to best ensure they are recommending facilitated coverage for medicines that are clinically or cost effective to ensure true patient access. This could be achieved by examining models such as coverage with evidence development, managed entry schemes, and new models around iterative payments based on performance that is re-assessed over time [20].

#### 4.1.3 Improve External and Internal Communication

Survey respondents reported a variable level of regulatory agency internal and external communication.

- Regulatory agencies should clearly communicate the criteria for pathway designation acceptance and withdrawal, disclose the designation selection process, and provide clear rationale and the reasons for designation refusal.
- Regulatory agencies should ensure internal alignment within divisions and across reviewers and experts to align on FRP adoption and ensure similar robustness of data is accepted.

In addition, although it was not mentioned by the survey respondents, communication also needs to include the recognition that further data will be needed to confirm or refute the initial findings regarding the product's safety and efficacy. Indeed, the company will need to continue to communicate new learnings about the product post-authorization as these confirmatory (or lack thereof) data are accrued.

#### 4.1.4 Increase Appropriate Use of FRPs

Increasing the appropriate use of FRPs would improve the level of regulatory agency experience with, and expertise in, these pathways.

- Regulatory agencies should encourage the use of existing regulatory pathways while developing additional alternatives to accelerated assessment or additional guidance

based on best practices observed from the use of established FRPs.

- Agencies should support the use of rolling submission and review, either where completed modules are submitted early and/or individual components of a module are provided to the agency reviewers giving the applicants an early opportunity to address data quality and potential review issues.

#### 4.1.5 Promote FRP Globalization

The lack of international alignment of FRPs presents a challenge to global development programs; staggered submissions risk limiting the expedited international availability of needed medicines.

- Agencies should collaborate to align the requirements and review practices of similar FRPs (e.g., BTD, PRIME, and Sakigake) to encourage harmonization and alignment of FRPs globally.
- Regulatory agencies should continue to work toward consensus on the definition and basic elements for FRPs to identify best practices for adoption of these pathways [21].

Overall, these recommendations support the need for continued agency–agency and agency–company discussions on aligning FRPs, which can benefit from better alignment on the criteria for unmet need and innovation. These have already started to take place, for example as directed by the EMA [22], as well as through International Coalition of Medicines Regulatory Authorities [23] and multistakeholder meetings [20, 24–26].

#### 4.2 Limitations

This survey was completed by a limited number of pharmaceutical companies, and all were considered large companies. Given this overrepresentation, the findings of this study could be further strengthened by applying the questionnaire to small- and medium-sized pharmaceutical and biotechnology companies, particularly given that a large percentage of early product development, which is when many of these FRPs can have their earliest positive impact, occurs in small start-ups, both biotech and otherwise. The aim would be to identify similarities and differences in perception compared with larger, more established organizations.

In addition, this study did not include the perceptions of patients/patient organizations regarding the FRPs in question. As these products are focused on meeting unmet medical needs, these organizations, which advocate for development of and access to products to meet those needs, would

provide views from critical stakeholders regarding the perceived value of these FRPs.

Another issue is the limited experience/data for PRIME and Sakigake for products that were submitted or approved. This is partially a reflection of the fact that both were more recently introduced than the FDA pathways, and that fewer products are designated by the EMA and PMDA than with the FDA annually. As a result, the challenges and opportunities highlighted for PRIME and Sakigake may evolve further over time, for example, whether the fact that the Sakigake designation requires that the asset be approved in Japan first and that its benefits may be overshadowed by conflict with global registration and pricing strategies and internal company resourcing. Therefore, it may be of interest to repeat this study, particularly for those two pathways, in a few years.

## 5 Conclusions

This study has highlighted some agency-specific recommendations for each of the FRPs. Interestingly, some of these recommendations are already being addressed by regulators, for example, greater cross-division and therapy collaboration for the FDA as part of the Office of New Drugs re-organization. This should further ensure the consistency in decision making by the FDA regarding FRPs in addition to the existing measures implemented by the agency, such as the use of the Medical Policy Council to assist BTD decision making by the review divisions. In addition, the current situation with COVID-19 has challenged agency processes to ensure even greater efficiency and flexibility for the use of FRPs, for example the shortening of EMA scientific advice time as well as employing a rolling submission process, both of which were options suggested in our questionnaire [27]. It will be interesting to see whether the changes introduced to agency processes and FRPs for COVID-19 treatments [14] will be implemented as part of the “new normal” into the FRPs in general to ensure more efficient and timelier product development and regulatory review of all important new medicines globally.

**Supplementary Information** The online version contains supplementary material available at <https://doi.org/10.1007/s40290-020-00372-7>.

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**Conflicts of interest** Magdalena Bujar, Neil McAuslane, and Lawrence Liberti have no conflicts of interest that are directly relevant to the content of this article.

**Ethics approval** As this research did not involve human subjects, ethics committee approval was not needed for the study.

**Availability of data and material** A copy of the questionnaire used in this study accompanies this report. Anonymized data related to the questionnaire responses are available upon reasonable request to the authors.

**Author contributions** MB designed the study, analyzed the data and wrote the manuscript; NM designed the study and critically reviewed the manuscript; LEL designed the study and critically reviewed the manuscript. All the authors have read and approved the final manuscript.

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## References

- Liberti L, Stolk P, McAuslane N, Somauroo A, Breckenridge AM, Leufkens HG. Adaptive licensing and facilitated regulatory pathways: a survey of stakeholder perceptions. *Clin Pharmacol Ther.* 2015;98:477–9. <https://doi.org/10.1002/cpt.140>.
- European Medicines Agency. European Medicines Agency Guidance for applicants seeking access to PRIME scheme. 2018. [https://www.ema.europa.eu/en/documents/other/european-medicines-agency-guidance-applicants-seeking-access-prime-scheme\\_en.pdf](https://www.ema.europa.eu/en/documents/other/european-medicines-agency-guidance-applicants-seeking-access-prime-scheme_en.pdf) EMA/191104/2015 Accessed 16 June 2020.
- US Food and Drug Administration. Guidance for industry expedited programs for serious conditions—drugs and biologics. 2014. <https://www.fda.gov/files/drugs/published/Expedited-Programs-for-Serious-Conditions-Drugs-and-Biologics.pdf> Accessed 16 June 2020.
- Pharmaceuticals and Medical Devices Agency. Strategy of Sakigake. 2014. <https://www.mhlw.go.jp/english/policy/health-medical/pharmaceuticals/dl/140729-01-01.pdf> Accessed 16 June 2020.
- Centre for Innovation in Regulatory Science. R&D Briefing 77: new drug approvals in six major authorities 2010–2019: Focus on facilitated regulatory pathways and internationalisation. 2020. <https://www.cirsci.org/publications/cirs-rd-briefing-77-new-drug-approvals-in-six-major-authorities/> Accessed 16 June 2020.
- Muensterman ET, Luo Y, Parker JM. Breakthrough therapy, PRIME and Sakigake: A comparison between neuroscience and oncology in obtaining preferred regulatory status. *Ther Innov Regul Sci.* 2019. <https://doi.org/10.1177/2168479019874062>.
- Nagai S. Flexible and expedited regulatory review processes for innovative medicines and regenerative medical products in the US, the EU and Japan. *Int J Mol Sci.* 2019;3:20.
- Liberti L, Bujar M, Breckenridge A, et al. Facilitated regulatory pathways: visualizing their characteristics, development, and authorization timelines. *Front Pharmacol.* 2017;8:161. <https://doi.org/10.3389/fphar.2017.00161>.
- Kesselheim AS, Wang B, Franklin JM, Darrow JJ. Trends in utilization of FDA expedited drug development and approval programs, 1987–2014: cohort study. *BMJ.* 2015;351:h4633. <https://doi.org/10.1136/bmj.h4633>.
- Kwok M, Foster T, Steinberg M. Expedited programs for serious conditions: an update on breakthrough therapy designation. *Clin Ther.* 2015;37:2104–20. <https://doi.org/10.1016/j.clinthera.2015.07.011>.
- Ehmann F, Papaluca AM, Salmonson T, et al. Gatekeepers and enablers: how drug regulators respond to a challenging and changing environment by moving toward a proactive attitude. *Clin Pharmacol Ther.* 2013;93:425–32. <https://doi.org/10.1038/clpt.2013.14>.
- Centre for Innovation in Regulatory Science. CIRS 2020 Agenda. 2020. <https://www.cirsci.org/> Accessed 16 June 2020.
- Pace J, Ghinea N, Kerridge I, Lipworth W. Demands for access to new therapies: are there alternatives to accelerated access? *BMJ.* 2017;359:j4494.
- Centre for Innovation in Regulatory Science. R&D Briefing 75—emergency use pathways (EUPs): Applying regulatory flexibility in the age of COVID-19. <https://www.cirsci.org/publications/cirs-rd-briefing-77-new-drug-approvals-in-six-major-authorities/> Accessed 16 June 2020.
- Lee M, Ly H, Möller CC, Ringel MS. Innovation in regulatory science is meeting evolution of clinical evidence generation. *Clin Pharmacol Ther.* 2019;105:886–98. <https://doi.org/10.1002/cpt.1354>.
- Kondo H, Hata T, Ito K, Koike H, Kono N. The current status of Sakigake designation in Japan, PRIME in the European Union and Breakthrough Therapy Designation in the United States. *Ther Innov Regul Sci.* 2017;51:51–4.
- Neez E, Hwang TJ, Sahoo SA, Naci H. European medicines Agency's priority medicines scheme at 2 years: an evaluation of clinical studies supporting eligible drugs. *Clin Pharmacol Ther.* 2020;107:541–52. <https://doi.org/10.1002/cpt.1669>.
- Farrimond B, Fleming JJ, Mathieu M. Accelerated pathways work—Now what? A survey of payers in the United States. *Ther Innov Regul Sci.* 2017;51:224–31. <https://doi.org/10.1177/2168479016668221>.
- Centre for Innovation in Regulatory Science. Workshop report—Identifying and understanding regulatory and reimbursement uncertainty during development. 9–10 October 2019, Surrey, UK.
- McAuslane N, Liberti L, Connelly P. The confluence of accelerated regulatory and health technology assessment access pathways. *Clin Pharmacol Ther.* 2019;105:935–42. <https://doi.org/10.1002/cpt.1315>.
- Liberti L, McAuslane N, Stolk P, Breckenridge A, Leufkens H. A proposed framework for a globally applicable pragmatic approach to using facilitated regulatory pathways. *Ther Innov Regul Sci.* 2020;54:55–68. <https://doi.org/10.1007/s43441-019-00029-x>.
- European Medicines Agency. Meeting Report: Workshop with stakeholders on support to quality development in early access approaches (i.e., PRIME, Breakthrough Therapies) 26 November 2018, European Medicines Agency, London. (2019). [https://www.ema.europa.eu/en/documents/report/report-workshop-stakeholders-support-quality-development-early-access-approaches-ie-prime\\_en.pdf](https://www.ema.europa.eu/en/documents/report/report-workshop-stakeholders-support-quality-development-early-access-approaches-ie-prime_en.pdf) Accessed 16 June 2020.
- International Coalition of Medicines Regulatory Authorities (ICMRA). Innovation strategic priority project report. 2019. <http://www.icmra.info/drupal/sites/default/files/2019-04/Innovation%20Strategic%20Priority%20Final%20Report.pdf> Accessed 16 June 2020

24. Vreman RA, Heikkinen I, Schuurman A, et al. Unmet medical need: an introduction to definitions and stakeholder perceptions. *Value Health*. 2019;22:1275–81.
25. Blumenrath S, Heikkinen I. What's in a name? Understanding unmet medical need may help align prioritization strategies. 2018. <https://www.clinicalleader.com/doc/what-s-in-a-name-understanding-unmet-medical-need-may-help-align-prioritization-strategies-0001> Accessed 16 June 2020.
26. Schulthess D, Baird LG, Trusheim M, et al. Medicines adaptive pathways to patients (MAPPs): a story of international collaboration leading to implementation. *Ther Innov Regul Sci*. 2016;50:347–54. <https://doi.org/10.1177/2168479015618697>.
27. European Medicines Agency. EMA initiatives for acceleration of development support and evaluation procedures for COVID-19 treatments and vaccines. 2020. [https://www.ema.europa.eu/en/documents/other/ema-initiatives-acceleration-development-support-evaluation-procedures-covid-19-treatments-vaccines\\_en.pdf](https://www.ema.europa.eu/en/documents/other/ema-initiatives-acceleration-development-support-evaluation-procedures-covid-19-treatments-vaccines_en.pdf) Accessed 16 June 2020